

**REMARKS**

***Status of the Claims***

Claims 1-14 are pending, with claims 1 and 6 being independent. Claims 6-10 and 12-14 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment. Claims 1 and 11 are amended herein. Claim 1 is amended to include subject matter from claim 13, and claim 11 is amended to address claim dependency. Support for the claim amendments can be found throughout the specification and claims as filed. As such, no new matter has been added.

Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks.

***Drawings***

Applicants note that corrected drawings containing English language translations of the original French figures were submitted with the application as-filed on September 29, 2005. Copies of the English figures are attached herewith for the convenience of the Office. Applicants further note that in the attached Figures clearer versions of figures 7B and 7C are included. If anything further is required in this regard, Applicants would be pleased to comply.

***Specification***

The specification is amended herein to provide a Brief Description of the Drawings section. Accordingly, this objection should be withdrawn.

***Claim Rejections Under 35 U.S.C. § 112, second paragraph***

Claims 1-5 and 14-15 stands rejected under 35 U.S.C. § 112, second paragraph, for the recitation of “affection”. Applicants note that the present English language specification was translated from the original French application. The use of the term “affection” is not a

fully accurate translation of the original French text. Accordingly, the word “affection” is replaced with “ailment”, as being the same word in French.

Thus, accordingly, this rejection should be withdrawn.

***Claim Rejections Under 35 U.S.C. § 112, first paragraph***

Claims 1-14 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly lacking enablement. Claims 6-10 and 12-14 are canceled herein without prejudice. Accordingly, this rejection is moot with regard to these claims.

With regard to the remaining claims, the Office states that the specification fails to demonstrate that diacerein increases the level of heme oxygenase (HO) *in vivo*. Applicants respectfully submit that the present specification provides sufficient guidance as to the relationship between diacerein and the corresponding increase seen in the level of HO. For example, references cited to in the specification demonstrate the expression of HO-1 (see specification, at pages 2-3).

Applicants further refer to U.S. Patent No, 6,066,333, issued on May 23, 2000, which relates to heme oxygenase activity and/or amount, and the use of compounds exhibiting such effect in the treatment of chronic inflammation. Finally, Applicants refer to the *in vivo* experiments described in the specification at page 9, line 10 to page 11, line 2.

In addition, the combination of diacerein with a well known COX-inhibitor or NSAID is also described in the present specification, at figures 13-15 and pages 11-13. For example, the combination of diacerein with rofecoxib, a major COX-2 inhibitor, is described.

Thus, Applicants submit that the specification in combination with what was known in the art show that diacerein (and rhein which is the metabolite of diacerein) provide the effect *in vivo* as claimed in the present application. Accordingly, this rejection should be withdrawn.

***Claim Rejections Under 35 U.S.C. § 102***

Claims 6-11 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Vittori et al. (WO 96/30034). Claims 6-10 are canceled herein without prejudice or disclaimer. The Office states that instant claims 6-11 are directed to a method of manufacturing a medicinal composition comprising rhein or rhein derivatives. However, claim 11, as now dependent on claim 5 via amendment, and ultimately claim 1, is directed to a method of treatment/prevention. Accordingly, Applicants submit the present rejection no longer applies to the subject matter of claim 11.

Claims 1-3, 5 and 14 stand rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Tamura et al. (*European Journal of Pharmacology*, Vol. 448). Claim 14 is canceled herein without prejudice or disclaimer.

Independent claim 1 is directed to a method of treatment or prevention of transplant rejection by increasing the levels of a heme oxygenase enzyme in a human or animal subject comprising administering a therapeutically effective amount of rhein or rhein derivative.

In contrast, Tamura merely discloses the already use of diacerein in the treatment of osteoarthritis. Its does not disclose the increase, or any other effect, on heme oxygenase. Further, Tamura fails to disclose any possible use of diacerein for the treatment or prevention of transplant rejection.

As Tamura fails to disclose the use of diacerein in the treatment of transplant rejection by increasing levels of the heme oxygenase enzyme, Tamura does not disclose all elements of the presently claimed invention.

Claim 12 stands rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Tamura et al. (*European Journal of Pharmacology*, Vol. 448). Claim 12 is canceled herein without prejudice or disclaimer.

Claims 1-3, 5 and 14 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Dahms et al. (*Drug Metabolism and Disposition*, Vol. 448). Claim 14 is canceled herein without prejudice or disclaimer.

Dahms relates to the side effects of rhein, and describes a study regarding various metabolites of rhein that may be detected in urine. Dahms does not disclose an effect on heme oxygenase. In fact, the study performed in Dahms does not concern heme oxygenase or any effect on heme oxygenase at all.

Dahms fails to disclose the use of diacerein in the treatment of transplant rejection by increasing levels of the heme oxygenase enzyme. Accordingly, Dahms does not disclose all elements of the presently claimed invention.

Claims 1-5 and 13-14 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Charbit et al. (U.S. Patent No. 6,610,750). Claim 14 is canceled herein without prejudice or disclaimer.

Charbit discloses the use of diacerein in the treatment of osteoarthritis, by delaying the progression of the destruction of the joint cartilage. However, Charbit does not disclose the use of diacerein in the treatment of transplant rejection by increasing levels of the heme oxygenase enzyme as recited by the present claims. Accordingly, Charbit does not disclose all elements of the presently claimed invention.

In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 102 be withdrawn.

#### ***Claim Rejections Under 35 U.S.C. § 103***

Claim 13 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Dahms in view of Häyry (Abstract). Claim 13 is canceled herein without prejudice or disclaimer.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Tamura. Claim 4, as dependent upon independent claim 1, is directed to the method of claim 1 wherein the rhein or rhein derivative is administered at a dose of 25 to 500 mg per day.

As noted above, Tamura does not recite all of the elements of claim 1, and accordingly does not recite all of the elements of dependent claim 4. Tamura does not disclose or suggest any other effect, on heme oxygenase, and certainly does not disclose or suggest an increase of HO. Further, Tamura fails to disclose any possible use of diacerein for the treatment or prevention of transplant rejection.

In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

***Double Patenting***

Claims 1-5 and 13-14 stand rejected under the grounds of nonstatutory obviousness-type double patenting as purportedly unpatentable over claims 1-6 of Charbit et al. (U.S. Patent No. 6,610,750). Applicants will consider a Terminal Disclaimer, as appropriate, upon identification of allowable subject matter.

Claims 1-5 and 13-14 stand provisionally rejected under the grounds of nonstatutory obviousness-type double patenting as purportedly unpatentable over claims 1-5 and 11-13 of copending U.S. Application No. 09/768,816. Applicants will consider a Terminal Disclaimer, as appropriate, upon identification of allowable subject matter.

**CONCLUSION**

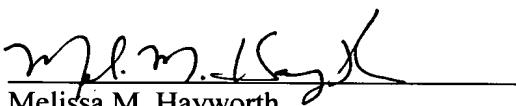
If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

Serial No. 10/522,035  
Amendment Dated: February 4, 2008  
Reply to Office Action Mailed: August 2, 2007  
Attorney Docket No. 99380.0117

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #99380.0117).

Respectfully submitted,

February 4, 2008

  
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**ATTACHMENT A**